4.2.0. Memory and Cognitive Impact of Foods

Research is proceeding apace rapidly on the connection between diet, including individual nutrients, on memory and other aspects of our thinking.

Most of the research to date has examined how foods relate to memory and cognition. This research has consisted of either animal studies of specific foods or nutrients, or of epidemiological studies of large groups of people (which can show an association, but not prove a direct cause). These studies have assessed explored the relationship between aspects of what we eat and the likelihood or risk of developing general cognitive problems, mild cognitive impairment (including of the amnestic type i.e. involving memory problems), any kind of dementia (i.e. problems in thinking in multiple areas serious enough to cause problems in daily life or work) or specific diseases such as Alzheimer's disease.

The mechanisms of action (for how specific foods might help or hurt the brain) identified to date appear to vary, and in the case of many whole foods, multiple actions could be working simultaneously (See for example, Emerson Lombardo NB et al. 2006, Sun AY et al 2008. Tian J et al 2010, Howes and Perry 2011, Williams RJ, 2011). These-Some ways specific foods could enhance brain health include increasing the availability of the memory neurotransmitter acetylcholine in the brain (apple juice, sage, Melissa, saffron) (e.g. by directly increasing production, slowing its metabolic breakdown, similar to the action of the cholinesterase inhibitors currently on the market), anti-oxidant and/or antiinflammatory action, regulating amount of various forms of Abeta peptides. slowing or preventing oligomerization or fibrilization of the Abeta molecule (Wang 2008, Frydman-Marom, A., 2011), protecting omega-3 fatty acids in brain cell membranes or fatty acids, regulating blood sugar and insulin, and/or cholesterol, estrogenic effects that can be neuro-protective, promoting creation of new brain cells or connective parts, or slowing their destruction, improving neuronal signaling and synapse activity, restoring mitochondrial function (related to energy) of brain cells, and retarding tau pathology (the "other" problem protein in AD) (Green 2007) as well as several others. This list is only partial!

The number of human clinical trials is still small but growing.

The body of evidence suggests a clear connection between foods, overall diet and our brain health, including memory and other cognitive skills such as attention and executive function (ability to organize and plan), and is growing each year.

This website and our brain healthy newsletters will keep you informed of this growing body of evidence.

Here are some highlights:

Several studies using various mouse models of Alzheimer's disease demonstrated the positive effects of a wide variety of foods substances thought to be chosen for their believed health benefits such as generally healthy, either from strong anti-oxidant properties or other features. Each food type may be comprised of thousands of nutrients. Foods tested that improved cognitive behaviors and/or lowered Abeta levels in TG mice include: apple juice, blueberries, spinach, strawberries, green tea, melatonin, DHA, plum juice, Concord grape juice, resveratrol, grape seed extract and others (Chan A et al, 2006, Rogers EJ et al.2004, Joseph JA. Et al. 1999, 2009, Lee JW, et al 2009, Mandel SA et al. 2011, Calon, F et al, 2004 and Green et al, 2007, Shukitt-Hale B et al, 2009, Shukitt-Hale B et al 2006, Lagouge, M., et al, 2006, Wang et al., 2008). Both almonds and walnuts helped Alzheimer transgenic mice perform better in cognitive tests and lowered levels of A-beta (Chauhan N et al. 2004, Muthaiyah B, et al, 2011 no published citation for almonds- see continued work by Neelima Chauhan, PhD, of the University of Illinois-Chicago, as reported in 2005 by Society for Neuroscience. http://www.sfn.org/index.aspx?pagename=news 111405). An unrelated Indian study in aged rats reported almond paste reversed scopolamine-induced amnesia, reduced cholinesterase activity in the brain, and also significantly reduced cholesterol and triglycerides in these aged rats (Kulkarni KS, et al. 2010).

Epidemiological studies have also identified a long list of brain healthy foods. More recently, innovative studies have begun to identify GROUPS of foods that appear to reduce risk of cognitive decline and onset of dementia, MCI or Alzheimer's disease, such as foods typical of the Mediterranean diet (Féart, C et al 2009, Gu Y, et al 2009, Scarmeas N et al., 2006, 2009a, 2009b, or the Dash DASH (Dietary Approaches to Stop Hypertension) Diet (LINK http://dashdiet.org/dash_diet_book.asp?google&gclid=CMDj8qOMsq0CFUTc4Aod_vz0FlQ_) (see unpublished study led by Heidi Wengreen, RD, PhD, Assistant Professor of Nutrition at Utah State University).

Combination supplement studies are <u>also</u> gaining interest. <u>Professor</u> Thomas Shea, <u>Ph.D.</u>, <u>Director of the Cellular Neurobiology and Neurodegeneration</u>

<u>Research Center</u>-at U Mass Lowell

(http://www.uml.edu/research labs/Cellular Neurobiology/Staff.html) is examining, first in mice and now in humans with and without memory impairments, a combination of certain B vitamins, and amino acids and antioxidants, with some encouraging results. Another study led by Jon Valla in Arizona uses a combination of fruit and vegetable powers, anti-inflammatory spices and herbs, and fish oil, yielding some positive results in TG mice. A similar combination with the addition of vitamin <u>E-D</u> is currently undergoing a pilot Phase I clinical trial with healthy older adults at Boston University. Also, Nutrictia,

a subsidiary of the French / Dannone Company, is pursuing human clinical trials in both Europe and the US, of Souvenaid® (http://souvenaid.com/) a combination of neuron building substrates identified (and patented) by Dr. Richard Wurtman at MIT, together with anti-oxidant isolated vitamins (Kamphuis and Scheltens, 2010), featured at a company sponsored symposium at MIT (http://web.mit.edu/newsoffice/2010/fighting-alzheimers.html). The consumer needs to be aware of the differences between medical foods such as Souvenaid, and nutritional supplements such as "Great Mind, as the rules of evidence and FDA regulations are different. The Alzheimer's Forum engaged in an excellent discussion of this topic in 2009, http://www.alzforum.org/new/detail.asp?id=2258

A Swedish placebo-controlled clinical trial using fish oil containing both DHA and EPA reported that fish oil appeared to slow cognitive decline only in a few persons with early stage Alzheimer's disease. In persons with mid stage disease the main positive effect was to reverse weight loss, which can be a serious problem in some people (Freund-Levi Y. et al, 2006). A larger, more recent clinical trial of just DHA derived from algae, in persons with AD, reported no significant effect on cognition; however the trial neglected to include EPA, the more highly anti-inflammatory long chain Omega 3 which, in nature, usually occurs in conjunction with DHA and which humans typically consume (and synthesize) along with DHA. Since other AD research has established that AD has an inflammatory aspect to its etiology, we believe that EPA may prove to be as important as DHA in its treatment and prevention. Also, psychiatric and attention-deficit disorders research has established that EPA rather than DHA appears to be the active long chain Omega 3 in achieving the desired treatment effect. See for example Jazayeri S, 2008

(http://www.ncbi.nlm.nih.gov/pubmed/18247193)

and work by Andew Stoll, MD (http://www.amazon.com/Omega-3-Connection-Groundbreaking-Anti-depression-Program/dp/0684871386) and Ned Hollowell, MD. (http://www.amazon.com/Delivered-Distraction-Getting-Attention-Disorder/dp/034544230X).

Cinnamon helps lower cholesterol and blood sugar, is a potent anti-oxidant (see ORAC chart...link) and is anti-inflammatory, and thus through these 4 pathways is thought to be positive for brain health. A January 2011 publication of an animal study (transgenic mice and flies) by a group of Israeli scientists suggests that cinnamon may also have a positive direct brain effect - cinnamon helps retard the development of Alzheimer's pathology by preventing the oligomerization ("clumping") of single Abeta molecules, leading to toxic forms that kill brain cells (Frydman-Marom A). To learn more, see our newsletter on the topic (Link to Cinnamon newsletter_ CHANGE THIS TO NEW WEBSITE POSITION http://healthcareinsights.net/home/newsletter-2011/august-2011newsletter/). Grape seed extract also prevents or slows oligomerization and fibrilization.

A proof of concept RCT in 12 older adults with MCI found significant improvements in one test of memory (verbal learning) in the 6 randomized to drinking Concord Grape Juice for 12 weeks (Krikorian R et al 2010).

Three small pilot randomized controlled studies of three different spices/herbs in Alzheimer's patients, all led by the same medical researcher in Iran, all published in reputable peer-reviewed journals, suggested positive effects in slowing cognitive decline compared to placebo (sage and lemon balm, also known as melissa) or slowing at same rate as a current prescription drug, without the usual gastro-intestinal side effects (saffron). (See_Akhondzadeh, S. et al. 2003a, 2003b, 2010)

Diets high in sugar and/or saturated fats appear to be harmful for the brain. A preclinical study in AD transgenic mice demonstrated that simply spiking water with 10% sugar (while offering same healthy mouse chow to two groups of identical, randomized mice) resulted in speedier cognitive decline of the mice drinking the sugared water, higher levels of Abeta in the brain, and abnormal cholesterol levels. Cao D et al. 2007, Suzanne Craft group's proof of concept randomized clinical trial in 50 older adults for just 1 month demonstrated that a high glycemic index, high saturated/high fat diet, compared to a low glycemic, low saturated fat/low fat diet, resulted in significantly worse cognitive performance (using a visual memory test), and undesirable changes in levels of Abeta in cerebral spinal fluid. (Bayer-Carter JL et al. 2011).

References:

Akhondzadeh S, Shafiee Sabet M, Harirchian MH, Togha M, Cheraghmakani H, et al. A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. Psychopharmacology (Berl). 2010 Jan; 207(4):637-43. Epub 2009 Oct 20.

Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. J Clin Pharm Ther. 2003 Feb;28(1):53-9.

Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi A, and Khani M. Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized, placebo controlled trial J Neurol Neurosurg Psychiatry. 2003 Jul;74(7):863-6.

Bayer-Carter JL, Green PS, Montine TJ, VanFossen B, Baker LD, Craft S, Diet Intervention and Cerebrospinal Fluid Biomarkers in Amnestic Mild Cognitive Impairment *Arch Neurol.* 2011;68(6):743-752. doi:10.1001/archneurol.2011.125

Calon, F., Lim, G.P., Yang, F., Morihara, T., Teter, B., Ubeda, O., Rostaing, P., Triller, A., Salem, Jr., N., Ashe, K.H., Frautschy, S.A., Cole, G.M., 2004. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. Neuron. 43, 633-645.

Cao D, Lu H, Lewis TL, Li L. Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. J Biol Chem, (2007) 282(50):36275-82. Epub 2007 Oct 17.

Chan A. Graves V. Shea TB. Apple juice concentrate maintains acetylcholine levels following dietary compromise. *J Alz. Dis.* 2006 *9* (3) :287-91.

Chauhan N, Wang KC, Wegiel J, Malik MN. Walnut extract inhibits the fibrillization of amyloid beta-protein, and also defibrillizes its preformed fibrils. Curr Alzheimer Res. 2004 Aug;1(3):183-8.

Emerson Lombardo, N.B., Volicer L., Martin A., Wu B., Zhang X.W., 2006. Memory preservation diet to reduce risk and slow progression of Alzheimer's disease, in Vellas, B., Grundman, M., Feldman, H., Fitten, L.J., Winblad, B. (Eds.), Research and Practice in Alzheimer's Disease and Cognitive Decline, vol 9, pp. 138-59.

Féart, C., Samieri, C., Barberger-Gateau, P., et al. Or Féart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, Scarmeas N, Barberger-Gateau P. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia *JAMA* 2009;302(6):638-648.

Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Palmblad J.et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch Neurol* 2006 *63*(10): 1402-8.

Frydman-Marom A, Levin A, Farfara D, Benromano T, Scherzer-Attali R, Peled S, Vassar R, Segal D, Gazit E, Frenkel D, Ovadia M. Orally administrated cinnamon extract reduces β -amyloid oligomerization and corrects cognitive impairment in Alzheimer's disease animal models. PLoS One. 2011 Jan 28;6(1):e16564

Green, K.N., Martinez-Coria, H., Khashwji, H., Hall, E.B., Yurko-Mauro, K.A., Ellis, L., LaFerla, F.M., 2007. Dietary docosahexaenoic acid and docosapentaenoic acid

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ameliorate amyloid- β and tau pathology via a mechanism involving Presenilin 1 levels. J Neurosci. 27(16), 4385-4395.

Gu Y, Luchsinger JA, Stern Y, Scarmeas N. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. *J Alzheimer's Dis.* (2010) *22*(2):483-92.

Howes MJ, Perry E. The role of phytochemicals in the treatment and prevention of dementia. Drugs Aging. 2011 Jun 1;28(6):439-68. doi: 10.2165/11591310-000000000-00000.

Jazayeri S, Tehrani-Doost M, Keshavarz SA, Hosseini M, Djazayery A, Amini H, Jalali M, Peet M. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder Aust N Z J Psychiatry. 2008 Mar;42(3):192-8

Joseph JA. Shukitt-Hale B. Casadesus G. Reversing the deleterious effects of aging on neuronal communication and behavior: beneficial properties of fruit polyphenolic compounds. [Review] [62 refs] *Am J Clin Nutr.* 2005 *81*(1 Suppl):313S-316S.

Joseph JA, Shukitt-Hale B, Denisova NA, Martin A, et al. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. *J-Neurosc:*1999 *19*(18): 8114-8121.

Kamphuis, P.J.G.H., Scheltens, P., 2010. Can nutrients prevent or delay onset of Alzheimer's disease? J Alzheimer's Dis. 20, 765-775.

Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. Br J Nutr. 2010 Mar;103(5):730-4. Epub 2009 Dec 23.

Kulkarni KS, Kasture SB, Mengi SA. Efficacy study of Prunus amygdalus (almond) nuts in scopolamine-induced amnesia in rats. Indian J Pharmacol. 2010 Jun;42(3):168-73.

Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C. Daussin, F., Messadeq, N., Milne, J., Lambert, P., Elliott, P., Geny, B., Laakso, M., Puigserver, P., Auwerx, J., 2006. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1a. Cell. 127, 1109-1122.

Lee JW, Lee YK, Ban JO, Ha TY, Yun YP, Han SB, Oh KW, Hong JT. Green tea (-)-epigallocatechin-3-gallate inhibits beta-amyloid-induced cognitive dysfunction through modification of secretase activity via inhibition of ERK and

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NF-kappaB pathways in mice. J Nutr. 2009 Oct;139(10):1987-93. Epub 2009 Aug 5.

Mandel SA, Amit T, Weinreb O, Youdim MB. Understanding the broad-spectrum neuroprotective action profile of green tea polyphenols in aging and neurodegenerative diseases. J Alzheimer's Dis. 2011;25(2):187-208.

Muthaiyah B, Essa MM, Chauhan V, Chauhan A. Protective effects of walnut extract against amyloid beta peptide-induced cell death and oxidative stress in PC12 cells. Neurochem Res. 2011 Nov;36(11):2096-103. Epub 2011 Jun 25.

Rogers EJ, Mihalick S, Ortiz D and Shea TB. Apple juice prevents oxidative stress and impaired cognitive performance caused by genetic and dietary deficiencies in mice. *J Nutr Health & Aging. 2004 8*:92-7.

Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, Stern Y. Physical activity, diet, and risk of Alzheimer disease. *JAMA* 2009b;302(6):627-637.

Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol Apr 18;2006 59(6):912–921. [PubMed: 16622828]

Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol. 2009a Feb;66(2):216-25.

Shukitt-Hale B, Kalt W, Carey AN, Vinqvist-Tymchuk M, McDonald J, Joseph JA. Plum juice, but not dried plum powder, is effective in mitigating cognitive deficits in aged rats. Nutrition. 2009 May;25(5):567-73. Epub 2008 Dec 18.

Shukitt-Hale B, Carey A, Simon L, Mark DA, Joseph JA. Effects of Concord grape juice on cognitive and motor deficits in aging. Nutrition. 2006 Mar;22(3):295-302. Epub 2006 Jan 18.

Sun AY, Wang Q, Simonyi A, Sun GY. Botanical phenolics and brain health. Neuromolecular Med. 2008;10(4):259-74. Epub 2008 Nov 1.

Tian J, Shi J, Zhang X, Wang Y. Herbal therapy: a new pathway for the treatment of Alzheimer's disease. Alzheimer's Res Ther. 2010 Oct 22;2(5):30.

Wang, J., Ho, L., Zhao, W., Ono, K., Rosenweig, C., Chen, L., Humala, N., Teplow, D.B., Pasinetti, G.M., 2008. Grape-derived polyphenolics prevent Aβ oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. J Neurosci. 28(25), 6388-6992.

Williams RJ, Spencer JP. Flavonoids, cognition, and dementia: Actions, mechanisms, and potential therapeutic utility for Alzheimer disease. Free Radic Biol Med. 2011 Sep 17. [Epub ahead of print]